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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,684	12/14/1999	REINER LAUS	7636-0020.30	4142

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/461,684	LAUS ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004 and 16 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/27/04 has been entered.

2. Applicant's amendment filed 7/16/04 is acknowledged and has been entered.

3. Applicant is reminded of Applicant's election of Group I (claims 1-7) and species of SEQ ID NO: 6.

Claims 1 and 4-7 read on the elected species, SEQ ID NO: 6.

Claims 1 and 4-7 are currently being examined to the extent they read upon the elected species SEQ ID NO: 6.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 5 is indefinite in the recitation of "where" in line 2 because it is not clear what is meant. It is suggested that Applicant amend said claim to recited "wherein".

b. Claim 6 recites "said one or more added peptidic sequences" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. Base claim 1 recites "an added peptidic sequence".

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejection set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly own at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1 and 4-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Buschle et al (PNAS USA 94: 3256-3261, 4/1997, IDS reference) in view of Kim et al (J. Immunol. 159(4): 1666-1668, 8/1997, previously provided).

Buschle et al teach that polycationic amino acids have been employed to enhance transport of proteins into cells and teach the ability of different cationic polymers, two of which are poly-Arg and poly-Lys, to transfer peptides to APCs (especially Abstract). Buschle et al teach compositions comprising antigenic peptides from pathogens and tumors and poly-Lys or poly-Arg (especially Abstract, Table 1 and page 3258, column 2 first full paragraph). Buschle et al teach that strongly augmented enhancement as only obtained with polyArg chains of 20 residues or more, thus in practice, polyArg chains of at least 15 amino acid residues are required for enhancing peptide delivery to cells. Buschle et al teach that polyArg is more efficient than polyLys at the same chain length (especially page 3259 at column 2). Buschle et al further teach that polyArg appears to act via an internalization-dependent mechanism, whereas polyLys appears to utilize permeabilization of the cell membrane (especially page 3261).

Buschle et al do not teach a composition comprising an antigen having an added peptidic sequence, wherein the added peptidic sequence is linked to the said antigen, nor wherein the antigen-polycationic sequence is a fusion protein.

Kim et al teach that because exogenous proteins do not ordinarily enter the cytosol [of APC] and access the MHC class I-processing pathway, protein-based vaccines that induce class I-restricted CTL responses have proved difficult to design. Kim et al further teach that they have addressed this problem by conjugating OVA antigen to a cationic peptide derived from HIV-1 tat which has a cysteine at the carboxy terminal end, and teach administration of a composition comprising the antigen/cationic peptide to APC leads to processing and presentation of the peptides in association with Class I MHC (especially Abstract). Kim et al

teach that loading of the OVA-tat required cytosolic proteolysis and transport of peptide into the ER (especially page 1667 at the second column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made an N-terminal cysteinylated peptide (as taught by Kim et al) version of the cationic poly-Lys or in particular the polyArg peptide taught by Buschle et al and to have conjugated it to one of the antigens taught by Buschle et al or Kim et al as taught by Kim et al for the antigen/cationic peptide of Kim et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to do this to enhance the transport of proteins or peptides from pathogens or tumors into the class I processing pathway and to stimulate CTL responses because Kim et al teach that protein-based vaccines that induce class I-restricted CTL responses have proved difficult to design and conjugation of an antigen to a cationic peptide leads to class I MHC processing and presentation, Buschle et al teach that polycationic amino acids have been employed to enhance transport of proteins into cells, the ability of different cationic polymers, two of which are poly-Arg and poly-Lys, to transfer peptides to APCs, and compositions comprising antigenic peptides from pathogens or tumors and further comprising poly-Lys or poly-Arg. Claim 5 is included in this rejection because claimed recitation of intended use in immunizing a subject against a tumor or pathogen wherein the antigen is specific to the tumor or antigen does not carry any patentable weight per se. A compound is the same compound irrespective of its intended use. Claim 7 is included in this rejection because the recitation of a method wherein the claimed product is made carries no patentable weight in this product claim.

Applicant's arguments in the amendment filed 7/16/04 have been fully considered but are not persuasive.

Applicant's position is of record on pages 5-8 in the said amendment.

It is the Examiner's position that Buschle et al teach that strongly augmented enhancement is only obtained with polyArg chains of 20 residues or more and thus in practice, polyArg chains of at least 15 amino acid residues are required for enhancing peptide delivery to cells, i.e., that one would have to use a polyArg chain of at least 15-20 amino acid residues to obtain good enhancement and that Kim et al did not obtain enhancement with a 9-mer polyLys peptide because it was not long enough. It is the Examiner's position that Buschle et al teach that their 20-mer polyArg peptide enhanced uptake of the antigen. It is the Examiner's position that Kim et al therefore does not teach away from the claimed invention. It is the Examiner's further position that Kim et al teach administration of an antigenic peptide coupled to an N-cysteinlyated cationic peptide for facilitation of the antigenic peptide into the Class I MHC processing and presentation pathway. It is the Examiner's position with regard to Applicant's argument that Applicant has clearly shown that the peptide sequences identified by SEQ ID NO: 1-9 improve uptake of an antigenic peptide from OVA into APC, and thus that Applicant has asserted a discovery beyond what was known in the art, that Applicant discloses

measurement of SEQ ID NO: 1, 2 and 3 in Examples 1 and 2 of the instant specification to show an improved uptake of an OVA antigenic peptide when conjugated to the said peptide over the level observed when antigenic peptide alone was used. SEQ ID NO: 1 is a 20-mer polyLys with an N-terminal Cys, whereas SEQ ID NO: 2 and 3 are not related to SEQ ID NO: 6. It is the Examiner's position that the polyLys peptide of the instant rejection as well as SEQ ID NO: 1 of the instant application are both 20-mers with an N-terminal Cys, and the art teaches enhancement using the said peptide. It is the Examiner's further position that Buschle et al has been argued separately by Applicant.

7. Claims 1 and 4-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US 2002/0077288 A1in view of Buschle et al (PNAS USA 94: 3256-3261, 4/1997, IDS reference) and US Patent No. 4,772,547.

US 2002/0077288 A1 discloses immunoconjugates of immunogenic or antigenic peptide covalently linked or "crosslinked" to an immunostimulatory polymer molecule consisting of 4-10 Lys or Arg residues at one or both of the amino and/or carboxy-termini of the peptide (especially [0027]-[0028] and [0040]. US 2002/0077288 A1 further discloses that the polyLys and polyArg cationic amino acid polymers have been used to enhance protein transport into cells, in particular, to enhance uptake of peptides by antigen presenting cells (APCs), thereby initiating an immune response[especially [0040]. US 2002/0077288 A1 discloses that peptide uptake mediated by polyLys may be due to an at least transient permeabilization of cell membranes and that peptide delivery in the presence of polyArg may rely on endocytic processes [especially [0040]. US 2002/0077288 A1 discloses that the immunogenic peptide is designed to avoid the problem of aggregation, i.e., the peptide is soluble (especially [0013]). US 2002/0077288 A1 discloses immunoconjugates may also be prepared using recombinant DNA techniques (especially [0064]-[0065]).

US 2002/0077288 A1 does not disclose a composition comprising an antigen having an added peptidic sequence consisting of the sequence of SEQ ID NO: 6, i.e., Cys-$[Arg]_{20}$.

Buschle et al teach that polycationic amino acids have been employed to enhance transport of proteins into cells and teach the ability of different cationic polymers, two of which are poly-Arg and poly-Lys, to transfer peptides to APCs (especially Abstract). Buschle et al teach compositions comprising antigenic peptides from pathogens and tumors and poly-Lys or poly-Arg (especially Abstract, Table 1 and page 3258, column 2 first full paragraph). Buschle et al teach that strongly augmented enhancement is only obtained with polyArg chains of 20 residues or more and that thus in practice, polyArg chains of at least 15 amino acid residues are required for enhancing peptide delivery to cells. Buschle et al teach that polyArg is more efficient than polyLys at the same chain length (especially page 3259 at column 2). Buschle et al further teach that polyArg appears to act via an inernalization-dependent mechanism, whereas polyLys appears to utilize permeabilization of the cell membrane (especially page 3261).

US Patent No. 4,772,547 discloses vaccine compositions comprising antigenic peptides or proteins from hepatitis surface antigen and HIV envelope and adjuvants such as IFN, IL-2, thymosin alpha 1 (i.e., immunopotentiating proteins) (especially column 8 at lines 25-49). US Patent No. 4,772,547 further discloses enhancing immunogenicity of the peptides by coupling the peptides covalently (via Cys, i.e., by "crosslinking") to toxoids or carrier materials that enhance immunogenicity.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the 20-mer polyArg taught by Buschle et al in the immunoconjugate disclosed by US 2002/0077288 A1 and to have crossliked it via Cys as disclosed by US Patent No. 4,772,547 for the antigenic peptide-enhancers of immunogenicity conjugates.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to initiate an effective immune response by producing an immunogenic conjugate capable of enhanced uptake of peptides as disclosed by US 2002/0077288 A1 using the 20-mer cationic polyArg taught by Buschle et al that has the highest efficacy in enhancing peptide delivery to cells and crosslinking it via the Cys taught by US Patent No. 4,772,547 because US Patent No. 4,772,547 discloses crosslinking via Cys.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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